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Discussion: Severe Mental Retardation and Cancer Among Atomic Bomb Survivors Exposed In Utero

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ABSTRACT When I was in medical school, Douglas Power Murphy, Professor of Obstetrics and Gynecology, told us of his inexpensive, simple study of "microcephaly" and mental retardation in newborn infants whose mothers had received therapeutic radiation early in pregnancy. His review of the literature and mail inquiry of other obstetrics centers in the United States revealed 14 published cases (Murphy, '28) and 16 unpublished (Goldstein and Murphy, '29). Here am I, 52 years later, still updating his findings. *Teratology 59:234–235, 1999.*

SEVERE MENTAL RETARDATION

"Microcephaly," now more properly called small head circumference, occurs alone at low doses, and with severe mental retardation (MR) at high doses. When magnetic resonance imaging (MRI) first became available at Fukuoka, 2 hr by train from Hiroshima, Schull arranged for the examination of five survivors with severe MR. Their gestational ages at exposure ranged from 8–15 weeks. Impaired development of the gray matter was most marked in two who were exposed in the 12–13 weeks of gestation. The least affected was exposed at 15 weeks. They were exposed, from youngest to oldest, to 0.86, 0.69, 1.64, 1.76, and 1.46 Gy (mother's uterine dose) (Schull et al., '91). Schull's recent statistical analysis of MR indicates that the threshold for severe MR, according to one mathematical model, is 0.57 Gy (CI 95% = 0.35–0.66 Gy) for those exposed at 8–15 weeks of gestation (Otake et al., '96). This finding contrasts with his original conclusion that the doubling dose for severe MR was 0.02 Gy (Otake and Schull, '84) and is now close to the clinically determined lowest dose to produce severe MR; namely 0.61 Gy, as shown in Figure 1. The data presented in Table 1 are in accord with a threshold of >0.50 Gy (Otake et al., '87).

CANCER

In a recent report, Delongchamp et al. ('97) reported on the 10 cancer deaths that have occurred among A-bomb survivors exposed in utero, concluding that the rate was remarkably similar to the risk of death from solid tumors (i.e., excluding leukemia) among children who were 0–5 years old at the time of exposure. Two of the deaths after intrauterine exposure were attributable to cancers not known to be induced by A-bomb exposure (Thompson et al., '95)–cancer of the pancreas after exposure to 1.08 Sv and uterine cancer after exposure at 2,194 m from the hypocenter–where the dose was <0.02 Sv.

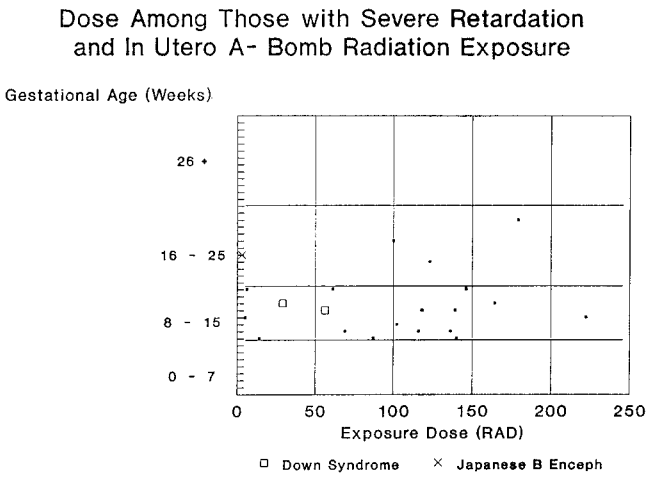

Fig. 1. Severe mental retardation among Hiroshima and Nagasaki atomic-bomb survivors exposed in utero, by gestational age and dose. Data from Otake et al. ('87).

Two of the remaining eight deaths were due to leukemia, after doses of 0.02 and 0.04 Sv (Table 2). The last-mentioned case occurred at age 30, long after exposure, instead of at less than age 10, when the excess of leukemia from maternal diagnostic X-ray examination of the abdomen during pregnancy has been reported (Stewart and Kneale, '68). The other deaths after doses of <0.10 Sv had colon cancer (exposed 1,956 m from the hypocenter) and breast cancer (0.09 Sv). Breast cancer is the most common radiation-induced cancer among female survivors (Miller and Boice, '97).

Of the four deaths from radiation-inducible cancers after doses of >0.10 Sv, a death from stomach cancer occurred after exposure to 0.24 Sv, and three cancer deaths occurred after doses of >0.49 Sv: 0.54 Sv

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TABLE 1. A-bomb survivors exposed at 8–15 weeks of gestational age: Numbers with severe mental retardation, at risk, and rate, by dose*

Dose	MR	At risk	Rate of MR
1.00+	12	26	1 in 2
0.50–0.99	4	43	1 in 11
0.10–0.49	2	215	1 in 100
0.005–0.09	3	212	1 in 70
<0.005	9	1,069	1 in 118

*MR, mental retardation.
Modified from Otake et al. ('96).

TABLE 2. A-bomb survivors exposed in utero: Numbers of cancer deaths by age 46, at risk, and cancer rate by dose category*

Dose (Sv)	Cancer	At risk	Cancer rate
0.50+	3	69	1 in 23
0.10–0.49	1	215	1 in 215
0.005–0.09	4	1,493	1 in 373

*Excludes two cancers not known to be induced by A-bomb exposure: pancreas (dose = 1.08 Sv) and uterus (dose = 2,194 m from hypocenter) (Thompson et al., '97). Numerators from Miller and Boice ('96), denominators from Otake et al. ('96).

(stomach cancer), 1.43 Sv (hepatocellular carcinoma at 6 years of age), and 2.24 Sv (ovarian cancer).

The distribution of cancer deaths by dose is shown in Table 2. Among the 69 exposed in utero to ≥0.50 Sv, three died of cancer before age 46. The frequency of 1 in 23 strongly suggests that the three cancers (stomach, liver, and ovary) were due to A-bomb exposure. The next lower dose category, 0.10–0.49 Sv, had only one cancer death (stomach after 0.24 Sv) among 215 at risk. The group at risk is small, so the role of radiation exposure in this case is open to question. The frequency is greater than that for survivors exposed to <0.005 Sv (1 in 1,281), but the intermediate group, exposed to 0.005–0.09 Sv had four cancer deaths among 212 at risk, a high rate that may be due to chance, given that three of the cancers occurred after doses lower than the lowest at which an excess can be detected among all A-bomb survivors (leukemia, 0.10 Sv; solid tumors, 0.05 Sv) according to Pierce et al. ('96). The remaining cancer, of the breast after exposure to 0.09, had a slightly higher dose than the minimum after which an excess of all solid tumors can be detected among all A-bomb survivors.

The evaluation by Delongchamp et al. ('97) concerned cancer deaths among survivors who had been exposed in utero to the A-bomb, only 69 of whom had received doses of >0.50 Sv. It would be valuable to know from statisticians at the Radiation Effects Research Foundation the lifetime number of cancer deaths expected among the small number of heavily exposed survivors at the normal rate, and how high the rate due to A-bomb exposure must be before a statistically significant excess can be detected.

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